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A useful magnesium reagent for the preparation of 1,1-difluoro-2-hydroxyphosphonates from diethyl bromodifluoromethylphosphonate via a metal-halogen exchange reaction

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Abstract

When $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Br}$ (**1**) is treated with isopropylmagnesium chloride in THF at low temperature it gives a magnesium species (**2**) which undergoes reactions with strong electrophiles (HCl , TMSCl , halogens, aldehydes and ketones). The formation of products strongly depends on the reaction conditions. With 1.5 equivalents of (**2**) between -78°C and 0°C , a conversion of more than 90% of aldehydes and ketones into 2-hydroxyphosphonates (**7**) and (**8**) can be achieved. These compounds (**7**) and (**8**) in the presence of base (NaH , LDA) are rearranged into 2,2-difluoroethylphosphates without concomitant formation of 1,1-difluoroolefines.

Key words : Isopropylmagnesium chloride, Metal-halogen exchange, Bromodifluorophosphonate, 1,1-Difluoro-2-hydroxyphosphonate.

1. Introduction

The metal-halogen exchange reaction is a valuable tool in organic synthesis, since it can be performed under mild conditions and usually with great efficiency [1]. In the chemistry of phosphonates we started to make use of the metal-halogen reaction with diethyl trichloromethylphosphonate which has been tested as a representative compound [2]. The successive exchange reactions of the three chlorine atoms by treatment with butyllithium and an appropriate electrophile in THF was used for the synthesis of functionalized phosphonates without any complications. With the use of isopropylmagnesium chloride the same trichloromethyl phosphonate can undergo the exchange reaction of only one chlorine atom to give the desired diethyl dichloromethylphosphonate [3]. To our knowledge it is still the best method for obtaining pure dichloromethylphosphonate in high yield. As we were developing the metal-halogen reaction as a synthetic tool, we became interested in the extension of the reductive dehalogenation reaction to diethyl bromodifluoromethylphosphonate **1** as well as in exploiting the synthetic potential of the magnesium species. Such a metal-bromine exchange reaction had already been performed on this reagent with Li , Zn and Cd as metal [4], we chose to perform it with Mg under mild conditions.

2. Results

Our study anticipated an easy access to diethyl bromodifluoromethylphosphonate **1**. This reagent was first prepared by Burton and Flynn *via* a Michaelis-Arbuzov type reaction from dibromodifluoromethane (CF₂Br₂) and triethylphosphite ((EtO)₃P) in refluxing Et₂O [5]; a long reaction time was required (24 h). Later the same reaction was reported as "a violent reaction which blew out the addition funnel, nitrogen inlet and stopper. This explosion could be controlled by running the reaction in a steel bomb" [6].

For our part we found that the synthesis of **1** could be achieved on a molar scale and in safe conditions by slow addition of pure (EtO)₃P to a solution of CF₂Br₂ in refluxing THF. Under these conditions CF₂Br₂ reacts readily, cleanly and quantitatively with (EtO)₃P. A ³¹P NMR spectroscopic investigation of the reaction mixture revealed that half an hour after the end of the addition (EtO)₃P was no longer detected and the only phosphorus species observed in the reaction mixture was diethyl bromodifluoromethylphosphonate **1** (δ ³¹P(THF) -0.4). A number of 1,1,1-trihalogenated phosphonates have been conveniently prepared according to this process which can be connected unambiguously to the Michaelis-Arbuzov reaction [7]. However among all the mechanistic pathways which are believed to be involved (ionic, radical and monoelectronic transfer) only the halophylic substitution (S_NCl⁺) has been retained as the major contribution [8].

Satisfied with the preparation of **1**, which was repeated with equal success several times, we decided to examine its reactivity. Diethyl bromodifluoromethylphosphonate **1** was treated at low temperature in THF with 1.1 equiv. of iPrMgCl. The magnesium-bromine exchange reaction was complete and the resultant magnesium compound **2** was obtained as a colorless, clear solution which could be stored at low temperature without any change. It is well known that diethyl lithiodifluoromethylphosphonate has to be kept at low temperature to prevent the thermal dissociation of the anion [4n, 9] when by contrast the organocadmium and organozinc reagents are remarkably stable at room temperature [4a, 4h]. The organomagnesium has an intermediate thermal stability. Effectively, when a cold solution of **2** in THF was slowly heated, the solution remained colorless until -40°C and then turned progressively brown. This transformation was monitored by following the change in the ³¹P NMR spectra of samples taken at various temperatures from -40°C and hydrolysed in acidic medium. They revealed a

decreasing intensity of the triplet corresponding to **3** indicating a slow decomposition of the magnesium species **2**.

The reactions of **2** were necessarily conducted at low temperature in order to prevent the anticipated decomposition. **2** reacts only with strong electrophiles such as aldehydes, ketones, halogens, chlorosilanes and mineral acid. This restricted reactivity is due to the poor nucleophilicity of the highly stabilized anion which moreover is thermally unstable above -40°C . Therefore, it seemed necessary to find out how the reaction conditions influenced yields and reactivities. Firstly we decided to examine two good electrophiles, the proton and chlorotrimethylsilane.

The production of diethyl difluoromethylphosphonate **3** strongly depended on the proton source. H_2O protonated the magnesium species **2** with only a reasonable yield (75%). It was clear that the strongly electron-withdrawing difluoro group considerably activated the phosphoryl group which is very sensitive to nucleophilic attacks [9]. A fast reaction with the electrophile at low temperature was required and thus the use of a dilute hydrochloric acid solution was preferred.

The complete conversion of **2** into **3** on preparative scale was achieved by pouring at low temperature a solution of **2** in a cold, stirred biphasic mixture of 3 M hydrochloric acid and CH_2Cl_2 ; with these conditions **3** could be isolated in a pure form and in good yield (85%). With chlorotrimethylsilane, the magnesium reagent **2** also underwent complete conversion into silylated compound to give **4** in excellent yield (90%) after treatment in acidic medium.

To get further insight in the synthetic potential of the magnesium species **2**, we also examined the reactivity of **2** with halogens (I_2) and halogenating agents (C_2Cl_6). With iodine in THF at low temperature iodination remained the main reaction, ($\delta^{31}\text{P}$ (THF) -1.4) (80%), but two by-products could be detected, we assumed that these compounds were **3** ($\delta^{31}\text{P}$ 4.9) and the difluoromethyl bis(diethylphosphonate) ($\delta^{31}\text{P}$ (THF) 3.4). After acidic work-up at low temperature the iododifluoromethylphosphonate (**6**) was isolated and purified by distillation (48%). With hexachloroethane at low temperature formation of chlorodifluoromethylphosphonate was the main reaction and the synthesis of (**5**) could be

achieved with reasonable yield (60%). This method of preparation of **5** and **6** is the most practical because attempts to prepare the compounds by reaction of Cl^- or I^- with **1** would give only dealkylation products by attack of the nucleophile on the phosphonate esters.

With aldehydes [10], the reaction parameters that we chose to study were *stoichiometry*, *temperature*, *reaction time* and *effect of lithium salts*. The metallation time was 5 min at -78°C in THF. The variation in stoichiometry **2** : aldehydes was tested for 1 : 1.1 and 1.5 : 1, the temperatures were -78°C to 0°C for one hour and 0°C to room temperature for an additional hour, and in addition some of the experiments were run under the influence of electrophilic assistance by lithium bromide in order to facilitate the condensation. The composition of the crude reaction mixture was determined by ^{31}P and ^1H NMR spectroscopy.

The addition of an aldehyde to **2** in stoichiometric ratio led to two phosphorus products, **7** and **3**, and unreacted aldehyde detected by ^1H NMR. For example, the 1,1-difluoro-2-hydroxyethylphosphonates **7e** and **7g** (Table 1) were isolated after treatment in acidic medium with respectively 70% and 60% yields. The amount of 1,1-difluoro-2-hydroxyphosphonate **7** was strongly dependant on the quantity of magnesium species **2**. The increase in the amount of **2** (1.5 equiv.), leads to a mixture of 1,1-difluoro-2-hydroxyethylphosphonate **7** with **3**, the ratios of which are dependant on the reaction conditions, but without any trace of aldehyde. With these new conditions the previously prepared 1,1-difluoro-2-hydroxyethylphosphonates **7e** and **7g** were isolated with respectively 85% and 96% yields (Table 1). With regard to these results, there is an increase in the yield of **7** with increasing number of equivalents of **2**. These conditions were extended to a large class of aldehydes both aliphatic, aromatic and heteroaromatic, and the results of these experiments are summarised in Table 2 .

Increasing the time of reaction between **2** and aldehydes led to a cleaner reaction, but omitting the heating step between 0°C and room temperature had a negative effect since formation of a third compound **13** took place. This was detected by ^{31}P NMR spectroscopy (δ ^{31}P (THF) +3.4) and isolated by hydrolysing the reaction mixture at an early stage. After column chromatography, a mixture of **7** and **13** with **13** as the minor product was obtained. Trituration with hexane allowed **13** contaminated with a small amount of **7** to be obtained. Thus **13** was attributed to difluoromethyl bis-(diethylphosphonate) in accordance with ^{19}F NMR spectroscopy (δ ^{19}F (CDCl_3) 122.0 (t, $^2J(\text{P-F}) = 87.6$)) and mass spectrum (m/z (IE) 324).

Performing the reaction between **2** and aldehydes in the presence of LiBr, in stoichiometric ratio, had a beneficial effect since the amount of 1,1-difluoro-2-hydroxyphosphonates **7** did not decrease by running the reaction at -40°C instead of -78°C. This is particularly obvious in the case of 4-methoxybenzaldehyde (Table 1 and Fig. 1), where the presence of LiBr made the formation of product **7g** easier, whereas decomposition mainly took place at the same temperature (-40°C) in the absence of LiBr.

TABLE 1. Effect of LiBr on the reaction of **2** with 4-methoxybenzaldehyde

Reaction temperature	Yields	
	without LiBr	with LiBr
- 78 °C	96 %	95 %
- 40 °C	partial decomposition	95 %
- 20 °C	major decomposition	major decomposition

Fig. 1. ^{31}P NMR spectra of the condensation reaction of **2** with 4-methoxybenzaldehyde under various experimental conditions.

We also examined the reactivity of ketones (Table 3). The metallation reaction was performed at -78°C , and the resulting magnesium species **2** was heated to -40°C and reacted at this temperature with ketones in a stoichiometric ratio of 1.5 : 1 in the presence of LiBr (1.5 equiv.). In spite of these conditions the conversion to the 1,1-difluoro-2-hydroxy-ethylphosphonate **8** was never complete and the maximum yield of these reactions was 82%.

TABLE 2. $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CH}(\text{OH})\text{R}^1$ **7**

Compd 7	R^1 -	Yields (%)
a	$-(\text{CH}_2)_6\text{CH}_3$	85 ^b
b	$-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	70 ^{a*}
c	$-\text{C}(\text{CH}_3)_3$	84 ^a
d	$-\text{CH}=\text{CHCH}_3$ (E)	89 ^b
e		85 ^b
f		95 ^b
g		96 ^b
h		92 ^b
i		94 ^b
j		96 ^b
k		82 ^b

Products are purified by distillation (a) or by chromatography (b).

* One diastereomer partially distilled with **3**

TABLE 3. $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{C}(\text{OH})\text{R}^1\text{R}^2$ **8**

Compound	$-\text{R}^1, \text{R}^2 -$	Yield (%)
a	$-(\text{CH}_2)_5 -$	72
b	$-(\text{CH}_2)_2 - \underset{\text{C}(\text{CH}_3)_3}{\underset{ }{\text{CH}}} - (\text{CH}_2)_2 -$	82
c		46
d		63

In addition, to get further information on the reactivity of the 1,1-difluoro-2-hydroxyethylphosphonates **7** and **8**, we explored their reactions with various bases (NaH, tBuOK, nBuLi and LDA). Our objective was to investigate the rearrangement reactions that they might undergo and to obtain 1,1-difluoroolefines on a preparative scale. There has been some previous work in this area and the initial observation of Obayashi et al. [4c], that lithiodifluoromethylphosphonate reacts with carbonyl compounds to produce 1,1-difluoroolefines, led us to examine the related chemistry of compounds **7** and **8**.

In THF at room temperature, the 1,1-difluoro-2-hydroxyethylphosphonate **7e** (Table 2) on reaction with NaH gave only the diethyl 2,2-difluoro-1-(4'-fluoro)phenylethylphosphate **9e** which was isolated in pure form with 61% yield. With tBuOK, even with a large excess, formation of **9e** remained the main reaction, but other by-products could be detected. With LDA and nBuLi in refluxing THF, there was formation of one major product the 1,1-difluoromethyl-(4'-fluoro)benzylalcohol **11e**, indicating that the prior rearrangement of **7e** into phosphate was followed by a loss of the phosphate moiety. By comparison the reaction was extended to **8a** (Table 3) and we observed that rearrangement to phosphate remained the main process. Rearrangement with NaH giving the best results, it has been extended to several 2-hydroxyphosphonates **7** (**a**, **b**, **c**, **e**, **f**, **g**, **h**, **k**, Table 2) and **8** (**a**, **c**, Table 3) in order to obtain the phosphates **9** and **10** which have been isolated with the following yields : **9a** (68%), **9b** (51%), **9c** (47%), **9e** (61%), **9f** (64%), **9g** (80%), **9k** (54%), **10a** (72%). However, in all the reported experiments, the desired 1,1-difluoroolefine was never detected except for **7h** (15%), and **8c** (20%).

3. Conclusion

When bromodifluoromethylphosphonate **1** is treated with iPrMgCl in THF and the resulting magnesium species **2**, reacted with an electrophile, the products formation will be influenced by stoichiometry, temperature and presence or absence of salts. The right balance between these three factors seems crucial for the synthetic applications of **2** and has led to the development of an efficient system for the formation of 1,1-difluoro-2-hydroxyethylphosphonates. However, the aim of this work was to improve the efficiency of the conditions

leading to the formation to 1,1-difluoroolefines. The reported results indicate that no improvement was obtained by using a step by step process and no additional benefit was achieved in comparison with previous results.

4. Experimental section

NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon and 81.01 MHz for phosphorus. ^{31}P downfield shifts (δ) are expressed with a positive sign, in ppm, relative to external 85% H_3PO_4 in H_2O . ^1H and ^{13}C chemical shifts (δ) are reported in ppm relative to CDCl_3 as internal standard. ^{19}F NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 235 MHz. ^{19}F chemical shifts (δ) are expressed in ppm with a positive sign relative to CFCl_3 as internal standard in CDCl_3 . Positive value of coupling constants (J) are given in Hertz. The following abbreviations are used: s, d, t, q, p, m for singlet, doublet, triplet, quadruplet, pentuplet and multiplet respectively.

Low-resolution mass spectra were recorded on a Hewlet Packard 5989 B mass spectrometer.

Organic solvents were purified by standard procedures. THF was distilled under an inert atmosphere from purple solutions of sodium: benzophenone ketyl. The synthesis of all compounds were carried out under dry nitrogen.

4.1. Diethyl 1,1-difluoro-1-bromomethylphosphonate **1**

A 1 L reactor equipped with a mechanical stirrer, thermometer, efficient reflux condenser, and an addition funnel was charged with dibromodifluoromethane (115 g, 0.55 mol) and THF (300 mL) and flushed with nitrogen. Stirring was initiated and the solution was warmed by immersing the flask in an oil bath heated at 60°C , triethyl phosphite (83 g, 0.5 mol) was then added dropwise over 1 h. After an additional 30 min at 60°C , the reaction mixture was cooled and the solvent was removed under reduced pressure. The crude product **1** (99 %) was purified by bulb-to-bulb distillation (b.p. $145\text{--}155^\circ\text{C}$ / 0.5 mm Hg). Yield = 96 %.

^{31}P NMR (CDCl_3): δ -2.6 (t, $^2J(\text{P-F}) = 93$) ; ^1H NMR (CDCl_3): δ 1.40 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.35 (qd, 4H, $^3J(\text{H-H}) = 7.1$, $^3J(\text{H-P}) = 8.2$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 17.0 (d, $^3J(\text{C-P}) = 5.8$, $\text{CH}_3\text{CH}_2\text{O}$), 67.0 (d, $^2J(\text{C-P}) = 6.4$, $\text{CH}_3\text{CH}_2\text{O}$), 117.3 (td, $^1J(\text{C-F}) = 328.9$, $^1J(\text{C-P}) = 238.2$, PCF_2Br).

m/z (EI) 269 ($\text{M}+\text{H}^+$, 5 %), 267 ($\text{M}+\text{H}^+$, 5 %), 137 (80), 109 (100).

4.2. Diethyl 1,1-difluoromethylphosphonate **3**

A 500 mL reactor equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel was charged with previously standardised $i\text{PrMgCl}$ (29 mL of 1.90 M Et_2O solution, 0.055 mol) and THF (120 mL). The solution was cooled to -78°C and a solution of **1** (13.4 g, 0.05 mol) in THF (50 mL) was added dropwise. The resulting mixture was stirred for 10 min at -78°C then at this temperature a solution of EtOH (10 mL) in THF (10 mL) was added dropwise. The reaction mixture was poured into an ice-cold mixture of HCl (40 mL of 3 M solution) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The extracts were dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product **3** which was purified by bulb-to-bulb distillation (b.p. $50-55^\circ\text{C}$ / 0.5 mmHg). Yield = 85 %.

^{31}P NMR (CDCl_3): δ +3.1 (t, $^2J(\text{P-F}) = 91$) ; ^1H NMR (CDCl_3): δ 1.36 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.26 (qd, 4H, $^3J(\text{H-H}) = 7.1$, $^3J(\text{H-P}) = 8.2$, $\text{CH}_3\text{CH}_2\text{O}$), 5.89 (td, 1H, $^2J(\text{H-F}) = 48.7$, $^2J(\text{H-P}) = 26.9$, PCF_2H) ; ^{13}C NMR (CDCl_3): δ 16.9 (d, $^3J(\text{C-P}) = 5.7$, $\text{CH}_3\text{CH}_2\text{O}$), 65.1 (d, $^2J(\text{C-P}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 112.0 (td, $^1J(\text{C-F}) = 257.9$, $^1J(\text{C-P}) = 213.6$, PCF_2H).

m/z (EI) 189 ($\text{M}+\text{H}^+$, 1 %), 137 (60), 160 (100).

4.3. Diethyl 1,1-difluoro-1-trimethylsilylmethylphosphonate **4**

A 500 mL reactor equipped as above was charged with $i\text{PrMgCl}$ (29 mL of 1.90 M Et_2O solution, 0.055 mol) and THF (120 mL). The solution was cooled to -78°C and a solution of **1** (13.4 g, 0.05 mol) and chlorotrimethylsilane (6 g, 0.055 mol) in THF (50 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78°C then poured into an ice-cold stirred mixture of HCl (40 mL of 3 M solution) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The extracts were dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product **4** which was purified by bulb-to-bulb distillation (b.p. $90-95^\circ\text{C}$ / 0.5 mm Hg). Yield = 90 %.

^{31}P NMR (CDCl_3): δ +7.7 (t, $^2J(\text{P-F}) = 92$) ; ^1H NMR (CDCl_3): δ 0.24 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.34 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.23 (qd, 4H, $^3J(\text{H-H}) = 7.1$, $^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ -4.8 (s, $\text{Si}(\text{CH}_3)_3$), 16.2 (d, $^3J(\text{C-P}) = 5.4$, $\text{CH}_3\text{CH}_2\text{O}$), 63.5 (d, $^2J(\text{C-P}) = 7.5$, $\text{CH}_3\text{CH}_2\text{O}$), 126.5 (td, $^1J(\text{C-F}) = 271.5$, $^1J(\text{C-P}) = 165.1$, $\text{PCF}_2\text{Si}(\text{CH}_3)_3$).

m/z (EI) 260 (M^+ , 2 %), 69 (100).

4.4. Diethyl 1,1-difluoro-1-chloromethylphosphonate **5**

A 250 mL reactor equipped as above was charged with $i\text{PrMgCl}$ (5.5 mL of 2.0 M Et_2O solution, 0.011 mol) and THF (10 mL). The solution was cooled to -78°C and a solution of **1** (2.67 g, 0.01 mol) in THF (15 mL) was added dropwise. The resulting mixture was stirred for

5 min at -78°C . Then a solution of hexachloroethane (2.61 g, 0.011 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C and then allowed to warm up to 0°C within 2 hours. It was poured into an ice-cold mixture of HCl (20 mL of 3 M solution) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The extracts were dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product **5** which was purified by bulb-to-bulb distillation (b.p. $50\text{--}55^{\circ}\text{C}$ / 0.5 mm Hg). Yield = 60 %.

^{31}P NMR (CDCl_3): δ -2.7 (t, $^2J(\text{P-F}) = 101$) ; ^1H NMR (CDCl_3): δ 1.37 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.31 (p, 4H, $^3J(\text{H-H}) = 7.1$, $^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 16.0 (d, $^3J(\text{C-P}) = 6.0$, $\text{CH}_3\text{CH}_2\text{O}$), 66.0 (d, $^2J(\text{C-P}) = 6.3$, $\text{CH}_3\text{CH}_2\text{O}$), 123.0 (td, $^1J(\text{C-F}) = 316.7$, $^1J(\text{C-P}) = 249.1$, PCF_2Cl).

m/z (EI) 223 (M^+ , 2 %), 137 (43), 109 (100).

4.5. Diethyl 1,1-difluoro-1-iodomethylphosphonate **6**

A 250 mL reactor equipped as above was charged with iPrMgCl (5.5 mL of 2.0 M Et_2O solution, 0.011 mol) and THF (10 mL). The solution was cooled to -78°C and a solution of **1** (2.67 g, 0.01 mol) in THF (15 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C . Then a solution of iodine (2.54 g, 0.011 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C and then allowed to warm up to 0°C within 2 hours. It was poured into an ice-cold mixture of HCl (20 mL of 3 M solution) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The extracts were washed with an aqueous sodium bisulfite solution, dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product **6** which was purified by bulb-to-bulb distillation (b.p. $95\text{--}100^{\circ}\text{C}$ / 0.5 mm Hg). Yield = 48 %.

^{31}P NMR (CDCl_3): δ -3.8 (t, $^2J(\text{P-F}) = 86$) ; ^1H NMR (CDCl_3): δ 1.39 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.34 (p, 4H, $^3J(\text{H-H}) = 7.1$, $^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 16.2 (d, $^3J(\text{C-P}) = 5.4$, $\text{CH}_3\text{CH}_2\text{O}$), 66.1 (d, $^2J(\text{C-P}) = 6.4$, $\text{CH}_3\text{CH}_2\text{O}$), 97.2 (td, $^1J(\text{C-F}) = 331.2$, $^1J(\text{C-P}) = 218.1$, PCF_2I).

m/z (EI) 315 ($\text{M}+\text{H}^+$, 3 %), 187 (60).

4.6. General procedure for the condensation of **2** with aldehydes

A 250 mL reactor equipped as above was charged with iPrMgCl (7.5 mL of 1.90 M Et_2O solution, 0.015 mol) and THF (20 mL). The solution was cooled to -78°C and a solution of **1** (4.00 g, 0.015 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C and at this temperature a solution of aldehyde (0.01 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C then was allowed to warm up to 0°C within one hour and from 0°C to room temperature for an additional hour.

The reaction mixture* was poured into an ice-cold mixture of HCl (20 mL of 2 M solution) and CH₂Cl₂ (20 mL). The aqueous layer was extracted with CH₂Cl₂ (2x20 mL). The extracts were dried (MgSO₄) and the solvents were removed under reduced pressure to give the crude product **7** mixed with **3** which was prior eliminated by heating the crude at 70 °C under 0.5 mm Hg for one hour. Then **7** was purified either by bulb-to-bulb distillation or by column chromatography (see Table 2).

* Work-up were performed in a different manner for the 2-(4'-dimethylamino)phenyl- (**7h**) and the 2-2'-pyridyl- (**7k**) phosphonates : Ice-cold HCl (7.5 mL of 2 M solution, 0.015 mol) was rapidly added to the reaction mixture of **7h** before extraction ; whereas the reaction mixture of **7k** was poured into an ice-cold mixture of saturated ammonium salt solution (20 mL) and CH₂Cl₂ (20 mL).

4.6.1. Diethyl 1,1-difluoro-2-heptyl-2-hydroxyethylphosphonate **7a**

³¹P NMR (CDCl₃): δ +5.4 (t, ²J(P-F) = 104) ; ¹⁹F NMR (CDCl₃): δ -116.8 (ddd, ²J(F-F) = 304.7, ²J(F-P) = 102.8, ³J(F-H) = 7.6, PCF_AFBCHOH), -125.6 (ddd, ²J(F-F) = 304.7, ²J(F-P) = 106.6, ³J(F-H) = 19.0, PCF_AEBCHOH) ; ¹H NMR (CDCl₃): δ 0.87 (t, 3H, ³J(H-H) = 6.3, (CH₂)₆CH₃), 1.29 (s, 8H, (CH₂)₄CH₃), 1.38 (t, 6H, ³J(H-H) = 7.1, CH₃CH₂O), 1.64 (m, 4H, CHOH(CH₂)₂), 3.4 (m, 1H, PCF₂CHOH), 3.9 (m, 1H, PCF₂CHOH), 4.29 (p, 4H, ³J(H-H) = ³J(H-P) = 7.1, CH₃CH₂O) ; ¹³C NMR (CDCl₃): δ 14.0 (s, (CH₂)₆CH₃), 16.3 (d, ³J(C-P) = 5.5, CH₃CH₂O), 22.7 (s, CH₂), 25.4 (s, CH₂), 28.9 (s, CH₂), 29.4 (d, ³J(C-P) = 7.5, CHOHCH₂), 29.8 (s, CH₂), 31.9 (s, CH₂), 64.6 (s, CH₃CH₂O), 71.2 (m, X part of ABMX system, ²J≈23.3, PMCF_AFBCH₂OH), 119.7 (ddd, X part of ABMX system, ¹J(C-F) = 268.6, ¹J(C-F) = 264.0, ¹J(C-P) = 207.6, PMCXFAFBCHOH).

m/z (EI) 317 (M+H⁺, 6 %), 188 (100), 161 (95).

4.6.2. Diethyl 1,1-difluoro-2-(2'-butyl)-2-hydroxyethylphosphonate (two diastereomers) **7b**

³¹P NMR (CDCl₃): δ +5.5 (t, ²J(P-F) = 105, P_{maj.}), +5.0 (dd, ²J(P-F) = 99 and 105, P_{min.}) ; ¹H NMR (CDCl₃): δ 0.89 (t, 3H, ³J(H-H) = 7.4, CH₂CH₃), 0.98 (d, 3H, ³J(H-H) = 6.7, CHCH₃), 1.35 (t, 6H, ³J(H-H) = 7.1, CH₃CH₂O), 1.5 (m, 2H, CH₂CH₃), 1.9 (m, 1H, CHOH-CH), 3.5 (m, 1H, PCF₂CHOH), 3.7 (m, 1H, PCF₂CHOH), 4.25 (m, 4H, ³J(H-H) = 7.1, CH₃CH₂O) ; ¹³C NMR (CDCl₃): δ 11.7 (s, CH₂CH₃ min.), 12.3 (s, CH₂CH₃ maj.), 14.1 (s, CHCH₃ maj.), 16.3 (s, CHCH₃ min.), 17.1 (d, ³J(C-P) = 5.3, CH₃CH₂O), 24.7 (s, CH₂CH₃ min.), 27.8 (s, CH₂CH₃ maj.), 34.9 (s, CHOH-CH_{maj.}), 35.7 (s, CHOH-CH_{min.}), 65.5 (s, CH₃CH₂O), 73.3 (m, CHOH_{maj.}), 75.3 (m, CHOH_{min.}), 120.9 (ddd, X part of ABMX system, ¹J(C-F) = 270.6, ¹J(C-F) = 265.4, ¹J(C-P) = 208.4, PMCXFAFBCHOH_{maj.}), 121.4 (ddd, X part of ABMX system, ¹J(C-F) = ¹J≈272.2, ¹J(C-F) = 266.0, ¹J(C-P) = 210.0, PMCXFAFBCHOH_{min.}).

m/z (EI) 274 (M^+ , 2 %), 217 (46), 188 (61), 161 (100).

4.6.3. Diethyl 1,1-difluoro-2-tertbutyl-2-hydroxyethylphosphonate **7c**

^{31}P NMR (CDCl_3): δ +5.8 (t, $^2J(\text{P-F}) = 104$) ; ^1H NMR (CDCl_3): δ 1.05 (d, 9H, $J = 0.9$, $\text{C}(\text{CH}_3)_3$), 1.36 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 3.5 (m, 1H, PCF_2CHOH), 3.71 (ddd, 1H, X part of ABMX system, $^3J(\text{C-P}) = 28.5$, $^3J(\text{C-F}) = 3.7$, $^3J(\text{C-F}) = 1.4$, $\text{P}_\text{M}\text{CF}_\text{A}\text{F}_\text{B}\text{CH}_\text{X}\text{OH}$), 4.27 (qd, 4H, $^3J(\text{H-P}) = 12.0$, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 17.0 (d, $^3J(\text{C-P}) = 5.7$, $\text{CH}_3\text{CH}_2\text{O}$), 27.3 (s, $\text{C}(\text{CH}_3)_3$), 36.0 (d, $\text{C}(\text{CH}_3)_3$), 65.2 (d, $^2J(\text{C-P}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 65.5 (d, $^2J(\text{C-P}) = 6.6$, $\text{CH}_3\text{CH}_2\text{O}$), 76.9 (m, X part of ABMX system, $^2J(\text{C-F}) = 24.9$, $^2J(\text{C-F}) = 20.8$, $^2J(\text{C-P}) = 10.0$, $\text{P}_\text{M}\text{CF}_\text{A}\text{F}_\text{B}\text{CH}_\text{X}\text{OH}$), 122.9 (m, X part of ABMX system, $^1J(\text{C-F}) = 277.0$, $^1J(\text{C-F}) = 267.4$, $^1J(\text{C-P}) = 209.2$, $\text{P}_\text{M}\text{CH}_\text{X}\text{F}_\text{A}\text{F}_\text{B}\text{CHOH}$).

m/z (EI) 275 ($M+\text{H}^+$, 100 %), 188 (19), 161 (56), 132 (39).

4.6.4. Diethyl 1,1-difluoro-2-(1'-propenyl)-2-hydroxyethylphosphonate **7d**

^{31}P NMR (CDCl_3): δ +5.0 (t, $^2J(\text{P-F}) = 103$) ; ^{19}F NMR (CDCl_3): δ -116.4 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $^3J(\text{F-H}) = 7.6$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -124.3 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.38 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.77 (d, 3H, $^3J(\text{H-H}) = 6.7$, $=\text{CHCH}_3$), 3.20 (d_{large} , 1H, $^3J(\text{H-H}) = 3.8$, PCF_2CHOH), 4.28 (p, 4H, $^3J(\text{H-P}) = 3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.4 (m, 1H, PCF_2CHOH), 5.59 (ddq, 1H, $^3J(\text{H-H})_{\text{trans}} = 15.4$, $^3J(\text{H-H}) = 6.5$, $^4J(\text{H-H}) = 1.5$, $\text{CH}=\text{CHCH}_3$), 5.95 (dq, 1H, $^3J(\text{H-H})_{\text{trans}} = 15.4$, $^3J(\text{H-H}) = 6.7$, $^4J(\text{H-H}) = 1.0$, $\text{CH}=\text{CHCH}_3$) ; ^{13}C NMR (CDCl_3): δ 16.3 (d, $^3J(\text{C-P}) = 5.2$, $\text{CH}_3\text{CH}_2\text{O}$), 17.9 (s, $=\text{CHCH}_3$), 64.7 (d, $^2J(\text{C-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 72.5 (ddd, X part of ABMX system, $^2J(\text{C-F}) = 25.8$, $^2J(\text{C-F}) = 22.8$, $^2J(\text{C-P}) = 15.1$, $\text{P}_\text{M}\text{CF}_\text{A}\text{F}_\text{B}\text{CH}_\text{X}\text{OH}$), 118.9 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 269.5$, $^1J(\text{C-F}) = 264.2$, $^1J(\text{C-P}) = 207.8$, $\text{P}_\text{M}\text{CH}_\text{X}\text{F}_\text{A}\text{F}_\text{B}\text{CHOH}$), 125.0 (d, $^3J(\text{C-P}) = 2.3$, $\text{CH}=\text{CHCH}_3$), 132.0 (s, $\text{CH}=\text{CHCH}_3$).

m/z (CI +ve) 259 ($M+\text{H}^+$, 100 %).

4.6.5. Diethyl 1,1-difluoro-2-(4'-fluorophenyl)-2-hydroxyethylphosphonate **7e**

^{31}P NMR (CDCl_3): δ +4.9 (t, $^2J(\text{P-F}) = 99$) ; ^{19}F NMR (CDCl_3): δ -113.7 (m, $\text{C}_6\text{H}_4\text{F}$), -115.0 (dd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -125.8 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.34 (2 t, 6H, $^3J(\text{H-H}) = 7.0$, $(\text{CH}_3\text{CH}_2\text{O})_\text{A and B}$), 4.0 (m, 1H, $\text{PCF}_2\text{CHOHC}_6\text{H}_4\text{F}$), 4.24 (qd, 4H, $^3J(\text{H-P}) = 8.1$, $^3J(\text{H-H}) = 7.0$, $(\text{CH}_3\text{CH}_2\text{O})_\text{A and B}$), 5.10 (ddd, 1H, $^3J(\text{H-P}) = 20.4$, $^3J(\text{H-F}) = 5.9$, $^3J(\text{H-F}) = 3.9$, $\text{PCF}_2\text{CHOHC}_6\text{H}_4\text{F}$), 7.07 (t, 2H, $^3J(\text{H-F}) = 3J(\text{H-H}) = 8.7$, H_{meta} of $\text{C}_6\text{H}_4\text{F}$), 7.46 (dd, 2H, $^3J(\text{H-H}) = 8.4$, $^4J(\text{H-F}) = 8.5$, H_{ortho} of $\text{C}_6\text{H}_4\text{F}$) ; ^{13}C NMR (CDCl_3): δ 17.0 (d, $^3J(\text{C-P}) = 5.7$, $\text{CH}_3\text{CH}_2\text{O}$), 65.7 (d, $^2J(\text{C-P}) = 6.8$, $\text{CH}_3\text{CH}_2\text{O}$), 73.3 (m 8 peaks, X part of ABMX

system, $^2J(\text{C-F}) = 26.4$, $^2J(\text{C-F}) = 21.6$, $^2J(\text{C-P}) = 14.4$, $\text{P}_\text{M}\text{CFAFB}\underline{\text{C}}\text{XHOH}$), 115.7 (d, $^2J(\text{C-F}) = 22.0$, $\underline{\text{C}}_\text{meta}$ of $\text{C}_6\text{H}_4\text{F}$), 118.6 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 271.9$, $^1J(\text{C-F}) = 264.9$, $^1J(\text{C-P}) = 206.2$, $\text{P}_\text{M}\underline{\text{C}}\text{XF}_\text{AFB}\text{CHOH}$), 130.6 (d, $^3J(\text{C-F}) = 8.1$, $\underline{\text{C}}_\text{ortho}$ of $\text{C}_6\text{H}_4\text{F}$), 131.5 (t, $^3J(\text{C-F}) = 3.0$, $\underline{\text{C}}_\text{ipso}$ of $\text{C}_6\text{H}_4\text{F}$), 163.7 (d, $^1J(\text{C-F}) = 249.6$, $\underline{\text{C}}_\text{para}$ of $\text{C}_6\text{H}_4\text{F}$).

m/z (EI) 312 (M^+ , 1 %), 188 (33), 161 (41), 132 (100).

4.6.6. Diethyl 1,1-difluoro-2-(4'-methylphenyl)-2-hydroxyethylphosphonate **7f**

^{31}P NMR (CDCl_3): δ +5.2 (t, $^2J(\text{P-F}) = 103$) ; ^{19}F NMR (CDCl_3): δ -114.8 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $^3J(\text{F-H}) = 7.6$, $\text{PCE}_\text{AFB}\text{CHOH}$), -125.6 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 106.6$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{AFB}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.31 (m, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 2.35 (s, 3H, $\text{C}_6\text{H}_4\text{CH}_3$), 4.1 (m_masked , 1H, PCF_2CHOH), 4.23 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$), 5.07 (ddd, 1H, $^3J(\text{H-P}) = 20.5$, $^3J(\text{H-F}) = 6.0$ et 3.8, PCF_2CHOH), 7.18 (d, 2H, $^3J(\text{H-H}) = 8.0$, H_meta of $\text{C}_6\text{H}_4\text{CH}_3$), 7.36 (d, 2H, $^3J(\text{H-H}) = 8.0$, H_ortho of $\text{C}_6\text{H}_4\text{CH}_3$) ; ^{13}C NMR (CDCl_3): δ 16.6 (d, $^3J(\text{C-P}) = 6.1$, $\underline{\text{C}}_\text{H}_3\text{CH}_2\text{O}$), 21.5 (s, $\text{C}_6\text{H}_4\text{CH}_3$), 65.0 (d, $^2J(\text{C-P}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 65.3 (d, $^2J(\text{C-P}) = 6.8$, $\text{CH}_3\text{CH}_2\text{O}$), 73.3 (ddd, X part of ABMX system, $^2J(\text{C-F}) = 26.5$, $^2J(\text{C-F}) = 21.3$, $^2J(\text{C-P}) = 14.7$, $\text{P}_\text{M}\text{CFAFB}\underline{\text{C}}\text{XHOH}$), 118.8 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 272.3$, $^1J(\text{C-F}) = 263.2$, $^1J(\text{C-P}) = 207.4$, $\text{P}_\text{M}\underline{\text{C}}\text{XF}_\text{AFB}\text{CHOH}$), 128.5 (s, $\underline{\text{C}}_\text{meta}$ of $\text{C}_6\text{H}_4\text{CH}_3$), 129.1 (s, $\underline{\text{C}}_\text{ortho}$ of $\text{C}_6\text{H}_4\text{CH}_3$), 133.1 (d, $^3J(\text{C-P}) = 5.7$, $\underline{\text{C}}_\text{ipso}$ of $\text{C}_6\text{H}_4\text{CH}_3$), 138.7 (s, $\underline{\text{C}}_\text{para}$ of $\text{C}_6\text{H}_4\text{CH}_3$).

m/z (EI) 308 (M^+ , 7 %), 188 (48), 161 (55), 132 (100).

4.6.7. Diethyl 1,1-difluoro-2-(4'-methoxyphenyl)-2-hydroxyethylphosphonate **7g**

^{31}P NMR (CDCl_3): δ +5.2 (t, $^2J(\text{P-F}) = 103$) ; ^{19}F NMR (CDCl_3): δ -115.2 (dd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $\text{PCE}_\text{AFB}\text{CHOH}$), -125.6 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{AFB}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.32 (td, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 3.80 (s, 3H, OCH_3), 4.0 (m, 1H, PCF_2CHOH), 4.18 (m, 4H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 5.06 (dm, 1H, $^3J = 20.2$, PCF_2CHOH), 6.90 (d, 2H, $^3J(\text{H-H}) = 8.6$, H_meta of $\text{C}_6\text{H}_4\text{OCH}_3$), 7.39 (d, 2H, $^3J(\text{H-H}) = 8.6$, H_ortho of $\text{C}_6\text{H}_4\text{OCH}_3$) ; ^{13}C NMR (CDCl_3): δ 16.5 (d, $^3J(\text{C-P}) = 4.6$, $\underline{\text{C}}_\text{H}_3\text{CH}_2\text{O}$), 55.5 (s, OCH_3), 65.2 (dd, $^2J(\text{C-P}) = 7.2$, $J = 12.0$, $\text{CH}_3\text{CH}_2\text{O}$), 73.3 (m, X part of ABMX system, $\text{P}_\text{M}\text{CFAFB}\underline{\text{C}}\text{XHOH}$), 113.8 (s, $\underline{\text{C}}_\text{meta}$ of $\text{C}_6\text{H}_4\text{OCH}_3$), 118.2 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 271.7$, $^1J(\text{C-F}) = 265.8$, $^1J(\text{C-P}) = 204.2$, $\text{P}_\text{M}\underline{\text{C}}\text{XF}_\text{AFB}\text{CHOH}$), 127.1 (t, $^3J(\text{C-F}) = 6.0$, $\underline{\text{C}}_\text{ipso}$ of $\text{C}_6\text{H}_4\text{OCH}_3$), 129.6 (s, $\underline{\text{C}}_\text{ortho}$ of $\text{C}_6\text{H}_4\text{OCH}_3$), 160.2 (s, $\underline{\text{C}}_\text{para}$ of $\text{C}_6\text{H}_4\text{OCH}_3$).

m/z (CI +ve) 324 (M^+ , 5 %).

4.6.8. Diethyl 1,1-difluoro-2-(4'-dimethylaminophenyl)-2-hydroxyethylphosphonate **7h**

^{31}P NMR (CDCl_3): δ +5.5 (t, $^2J(\text{P-F}) = 104$) ; ^{19}F NMR (CDCl_3): δ -115.2 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $^3J(\text{F-H}) = 7.6$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -125.5 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 106.6$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.33 (td, 6H, $^3J(\text{H-H}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 2.95 (s, 6H, $\text{N}(\text{CH}_3)_2$), 4.0 (m, 1H, PCF_2CHOH), 4.24 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$), 5.03 (dm, 1H, $^3J(\text{H-P}) = 20$, PCF_2CHOH), 6.72 (d, 2H, $^3J(\text{H-H}) = 8.8$, H_meta of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$), 7.33 (d, 2H, $^3J(\text{H-H}) = 8.3$, H_ortho of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$) ; ^{13}C NMR (CDCl_3): δ 17.0 (d, $^3J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 41.1 (s, $\text{N}(\text{CH}_3)_2$), 65.5 (dd, $^2J(\text{C-P}) = 6.7$, $J = 12.1$, $\text{CH}_3\text{CH}_2\text{O}$), 73.8 (m, X part of ABMX system, $^2J(\text{C-F}) = 26.6$, $^2J(\text{C-F}) = 21.3$, $^2J(\text{C-P}) = 14.7$, $\text{PMCF}_\text{A}\text{F}_\text{B}\text{CXHOH}$), 112.6 (s, C_meta of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$), 118.8 (m, X part of ABMX system, $^1J(\text{C-F}) = 270.1$, $^1J(\text{C-F}) = 264.0$, $^1J(\text{C-P}) = 204.5$, PMCXFAFBCHOH), 123.0 (d, $^3J(\text{C-P}) = 4.9$, C_ipso of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$), 129.6 (s, C_ortho of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$), 151.6 (s, C_para of $\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$).

m/z (EI) 337 (M^+ , 7 %), 150 (100).

4.6.9. Diethyl 1,1-difluoro 2-(2'-furyl) 2-hydroxyethylphosphonate **7i**

^{31}P NMR (CDCl_3): δ +4.3 (t, $^2J(\text{P-F}) = 101$) ; ^{19}F NMR (CDCl_3): δ -115.9 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $^3J(\text{F-H}) = 7.6$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -123.6 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.34 (td, 6H, $^3J(\text{H-H}) = 7.0$, $^4J(\text{H-P}) = 4.5$, $\text{CH}_3\text{CH}_2\text{O}$), 4.09 (m, 1H, PCF_2CHOH), 4.25 (qd, 4H, $^3J(\text{H-P}) = 8.9$, $^3J(\text{H-H}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 5.15 (dm, 1H, PCF_2CHOH), 6.40 (dd, 1H, $^3J(\text{H-H}) = 3.3$, $^3J(\text{H-H}) = 1.8$, H_4 of $\text{C}_4\text{H}_3\text{O}$), 6.52 (d_large , 1H, $^3J(\text{H-H}) = 3.3$, H_3 of $\text{C}_4\text{H}_3\text{O}$), 7.45 (m, 1H, H_5 of $\text{C}_4\text{H}_3\text{O}$) ; ^{13}C NMR (CDCl_3): δ 16.6 (d, $^3J(\text{C-P}) = 6.0$, $\text{CH}_3\text{CH}_2\text{O}$), 65.4 (d, $^2J(\text{C-P}) = 6.5$, $\text{CH}_3\text{CH}_2\text{O}$), 68.1 (ddd, X part of ABMX system, $^2J(\text{C-F}) = 27.1$, $^2J(\text{C-F}) = 21.9$, $^2J(\text{C-P}) = 16.6$, $\text{PMCF}_\text{A}\text{F}_\text{B}\text{CXHOH}$), 110.3 (s, C_3 of $\text{C}_4\text{H}_3\text{O}$), 110.9 (s, C_4 of $\text{C}_4\text{H}_3\text{O}$), 118.3 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 271.7$, $^1J(\text{C-F}) = 265.0$, $^1J(\text{C-P}) = 209.8$, PMCXFAFBCHOH), 143.3 (s, C_5 of $\text{C}_4\text{H}_3\text{O}$), 149.6 (dd, $^3J(\text{C-P}) = 6.2$, $^3J(\text{C-P}) = 2.7$, C_2 of $\text{C}_4\text{H}_3\text{O}$).

m/z (EI) 284 (M^+ , 10 %), 188 (73), 161 (75), 132 (100).

4.6.10. Diethyl 1,1-difluoro 2-(2'-thienyl) 2-hydroxyethylphosphonate **7j**

^{31}P NMR (CDCl_3): δ +4.8 (t, $^2J(\text{P-F}) = 101$) ; ^{19}F NMR (CDCl_3): δ -115.0 (ddd, $^2J(\text{F-F}) = 299.0$, $^2J(\text{F-P}) = 99.0$, $^3J(\text{F-H}) = 7.6$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -125.2 (ddd, $^2J(\text{F-F}) = 299.0$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.34 (q, 6H, $^3J(\text{H-H}) = 7.0$, $^4J(\text{H-P}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 1.8 (m, 1H, PCF_2CHOH), 4.25 (p, 4H, $^3J(\text{H-P}) = 7.0$, $^3J(\text{H-H}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 5.39 (dm, 1H, $^3J(\text{H-P}) = 19.5$, PCF_2CHOH), 7.03 (dd, 1H, $^3J(\text{H-H}) = 5.0$, $^3J(\text{H-H}) = 3.6$, H_4 of $\text{C}_4\text{H}_3\text{S}$), 7.18 (d, 1H, $^3J(\text{H-H}) = 3.6$, H_3 of $\text{C}_4\text{H}_3\text{S}$), 7.36 (dd, 1H, $^3J(\text{H-H}) = 5.0$, $^4J(\text{H-H}) = 1.2$, H_5 of $\text{C}_4\text{H}_3\text{S}$) ; ^{13}C NMR (CDCl_3): δ 16.9 (d, $^3J(\text{C-P}) = 5.6$, $\text{CH}_3\text{CH}_2\text{O}$),

65.7 (d, $^2J(\text{C-P}) = 7.0$, $\text{CH}_3\text{CH}_2\text{O}$), 70.7 (ddd, X part of ABMX system, $^2J(\text{C-F}) = 27.5$, $^2J(\text{C-F}) = 22.4$, $^2J(\text{C-P}) = 16.2$, $\text{P}(\text{MCF}_\text{A}\text{F}_\text{B}\text{C}_\text{X}\text{HOH})$), 118.1 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 272.6$, $^1J(\text{C-F}) = 264.8$, $^1J(\text{C-P}) = 206.6$, $\text{P}(\text{MC}_\text{X}\text{F}_\text{A}\text{F}_\text{B}\text{CHOH})$), 127.1 (s, C_3 of $\text{C}_4\text{H}_3\text{S}$), 127.2 (s, C_4 of $\text{C}_4\text{H}_3\text{S}$), 127.7 (s, C_5 of $\text{C}_4\text{H}_3\text{S}$), 138.4 (d, $^3J(\text{C-P}) = 6.7$, C_2 of $\text{C}_4\text{H}_3\text{S}$).

m/z (EI) 300 (M^+ , 13 %), 188 (80), 161 (93), 132 (100).

4.6.11. Diethyl 1,1-difluoro 2-(2'-pyridyl) 2-hydroxyethylphosphonate **7k**

^{31}P NMR (CDCl_3): δ +4.3 (t, $^2J(\text{P-F}) = 101$) ; ^{19}F NMR (CDCl_3): δ -114.6 (dd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 99.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$), -125.6 (ddd, $^2J(\text{F-F}) = 304.7$, $^2J(\text{F-P}) = 102.8$, $^3J(\text{F-H}) = 19.0$, $\text{PCF}_\text{A}\text{F}_\text{B}\text{CHOH}$) ; ^1H NMR (CDCl_3): δ 1.35 (td, 6H, $^3J(\text{H-H}) = 7.1$, $^4J(\text{H-P}) = 2.7$, $\text{CH}_3\text{CH}_2\text{O}$), 4.26 (qd, 4H, $^3J(\text{H-P}) = 8.0$, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 5.20 (dt, 1H, $^3J(\text{H-P}) = 20.8$, $^3J(\text{H-F}) = 4.5$, PCF_2CHOH), 5.67 (s_{large} , 1H, PCF_2CHOH), 7.35 (dd, 1H, $^3J(\text{H-H}) = 7.7$ et 4.8, H_5 of $\text{C}_5\text{H}_4\text{N}$), 7.48 (d_{large} , 1H, $^3J(\text{H-H}) = 7.7$, H_3 of $\text{C}_5\text{H}_4\text{N}$), 7.78 (tt, 1H, $^3J(\text{H-H}) = 7.7$, $^4J(\text{H-H}) = ^6J(\text{H-P}) = 1.2$, H_4 of $\text{C}_5\text{H}_4\text{N}$), 8.60 (dd, 1H, $^3J(\text{H-H}) = 4.8$, $^4J(\text{H-H}) = 1.2$, H_6 of $\text{C}_5\text{H}_4\text{N}$) ; ^{13}C NMR (CDCl_3): δ 15.9 (d, $^3J(\text{C-P}) = 5.4$, $\text{CH}_3\text{CH}_2\text{O}$), 64.3 (d, $^2J(\text{C-P}) = 6.3$, $\text{CH}_3\text{CH}_2\text{O}$), 72.5 (ddd, X part of ABMX system, $^2J(\text{C-F}) = 26.1$, $^2J(\text{C-F}) = 21.9$, $^2J(\text{C-P}) = 13.6$, $\text{P}(\text{MCF}_\text{A}\text{F}_\text{B}\text{C}_\text{X}\text{HOH})$), 118.4 (ddd, X part of ABMX system, $^1J(\text{C-F}) = 272.6$, $^1J(\text{C-F}) = 264.8$, $^1J(\text{C-P}) = 209.2$, $\text{P}(\text{MC}_\text{X}\text{F}_\text{A}\text{F}_\text{B}\text{CHOH})$), 123.0 (s, C_3 of $\text{C}_5\text{H}_4\text{N}$), 123.5 (s, C_5 of $\text{C}_5\text{H}_4\text{N}$), 136.5 (s, C_4 of $\text{C}_5\text{H}_4\text{N}$), 147.9 (s, C_6 of $\text{C}_5\text{H}_4\text{N}$), 153.9 (d, $^3J(\text{C-P}) = 6.1$, C_2 of $\text{C}_5\text{H}_4\text{N}$).

m/z (EI) 296 ($\text{M} + \text{H}^+$, 5 %), 161 (8), 132 (17), 108 (100).

4.7. General procedure for the condensation of **2** with ketones

A 250 mL reactor equipped as above was charged with anhydrous LiBr (1.31 g, 0.015 mol, dried by heating at 150°C under 0.1 mm Hg vacuum over one hour) and THF (15 mL) and heated at 50°C until complete dissolution. $i\text{PrMgCl}$ (7.5 mL of 1.90 M Et_2O solution, 0.015 mol) and THF (10 mL) were added into the reactor at -20°C . The solution was cooled to -78°C and a solution of **1** (4.00 g, 0.015 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 5 min at -78°C then allow to warm up to -40°C . At this temperature a solution of ketone (0.01 mol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 15 min at -40°C then was allowed to warm up to 0°C within one hour and from 0°C to room temperature for an additional hour. The reaction mixture was poured into an ice-cold mixture of HCl (20 mL of 2 M solution) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The extracts were dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product **8** and the excess of **3** which was prior eliminated by heating the crude mixture at 70°C under 0.5 mm Hg for

one hour. Then **8** was purified either by bulb-to-bulb distillation or by column chromatography (see Table 3).

4.7.1. Diethyl 1,1-difluoro 1-(1'-hydroxy)cyclohexyl methylphosphonate **8a**

^{31}P NMR (CDCl_3): δ +5.5 (t, $^2J(\text{P-F}) = 107$) ; ^{19}F NMR (CDCl_3): δ -121.5 (d, $^2J(\text{F-P}) = 106.6$, PCF_2COH) ; ^1H NMR (CDCl_3): δ 1.2 (m, 1H, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 1.37 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.61 (m, 7H, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 1.87 (d_{large}, 2H, $^2J(\text{H-H}) = 11.9$, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_2$), 2.99 (s, 1H, PCF_2COH), 4.28 (p, 4H, $^3J(\text{H-P}) = ^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 16.9 (d, $^3J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 21.1 (s, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 26.0 (s, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 30.3 (d, $^3J(\text{C-P}) = 2.7$, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 65.5 (d, $^2J(\text{C-P}) = 6.8$, $\text{CH}_3\text{CH}_2\text{O}$), 74.5 (td, $^2J(\text{C-F}) = 20.9$, $^2J(\text{C-P}) = 13.4$, PCF_2COH), 120.9 (td, $^1J(\text{C-F}) = 271.0$, $^1J(\text{C-P}) = 200.3$, PCF_2COH).

m/z (EI) 287 ($\text{M}+\text{H}^+$, 6 %), 188 (100), 161 (90), 132 (79).

4.7.2. Diethyl 1,1-difluoro 1-(1'-hydroxy-4'-tertbutyl)cyclohexyl methylphosphonate **8b**

^{31}P NMR (CDCl_3): δ +5.6 (t, $^2J(\text{P-F}) = 106$) ; ^{19}F NMR (CDCl_3): δ -121.5 (d, $^2J(\text{F-P}) = 106.6$, PCF_2COH) ; ^1H NMR (CDCl_3): δ 0.93 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.05 (t_{large}, 1H, $^3J(\text{H}_{\text{ax}}-\text{H}_{\text{ax}}) = 11.4$, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_{\text{ax}}$), 1.45 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.52-1.75 (m, 6H, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_{\text{ax}}$), 2.01 (d_{large}, 2H, $^2J(\text{H-H}) = 12.4$, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_{\text{ax}}$), 2.85 (s_{large}, 1H, PCF_2COH), 4.36 (p, 4H, $^3J(\text{H-P}) = ^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$) ; ^{13}C NMR (CDCl_3): δ 17.0 (d, $^3J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 22.0 (s, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}$), 28.1 (s, $\text{C}(\text{CH}_3)_3$), 30.8 (d, $^3J(\text{C-P}) = 2.3$, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}$), 33.3 (s, $\text{C}(\text{CH}_3)_3$), 48.0 (s, $\text{CHC}(\text{CH}_3)_3$), 65.5 (d, $^2J(\text{C-P}) = 6.9$, $\text{CH}_3\text{CH}_2\text{O}$), 74.3 (td, $^2J(\text{C-F}) = 20.8$, $^2J(\text{C-P}) = 13.3$, PCF_2COH), 121.0 (td, $^1J(\text{C-F}) = 270.9$, $^1J(\text{C-P}) = 200.4$, PCF_2COH).

m/z (CI +ve) 343 ($\text{M}+\text{H}^+$, 100 %).

4.7.3. Diethyl 1,1-difluoro 1-(1'-hydroxy-1',2',3',4'-tetrahydro)naphthyl methylphosphonate **8c**

^{31}P NMR (CDCl_3): δ +5.4 (dd, $^2J(\text{P-F}) = 133$ and 99) ; ^1H NMR (CDCl_3): δ 1.31 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 1.36 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 1.8 - 2.0 (m, 3H, $\text{H}_{3'}$ and $\text{H}_{2'}$ pseudo eq), 2.5 (m, 1H, $\text{H}_{2'}$ pseudo ax), 2.79 (t, 2H, $^3J(\text{H-H}) = 6.0$, $\text{H}_{4'}$), 3.29 (s, 1H, PCF_2COH), 4.2 (m, 2H, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 4.26 (p, 2H, $^3J(\text{H-P}) = ^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 7.10 (m, 1H, $\text{H}_{6'}$), 7.23 (m, 2H, $\text{H}_{5'}$ and $7'$), 7.75 (m, 1H, $\text{H}_{8'}$). ; ^{13}C NMR (CDCl_3): δ 16.4 (d, $^3J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 18.8 (d, $^4J(\text{C-P}) = 3.4$, $\text{C}_{3'}$), 29.4 (s, $\text{C}_{4'}$), 33.8 (d, $^3J(\text{C-P}) = 3.7$, $\text{C}_{2'}$), 64.6 (d, $^2J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 73.7 (q, $^2J(\text{C-F}) = 20.7$, $^2J(\text{C-P}) = 17.5$, PCF_2COH), 111.6 (q, $^1J(\text{C-F}) = 257.8$, $^1J(\text{C-P}) = 212.3$, PCF_2COH), 125.7 (s, $\text{C}_{6'}$), 128.3 (s, $\text{C}_{7'}$), 128.7 (s, $\text{C}_{5'}$), 129.4 (d, $^4J(\text{C-P}) = 2.9$, $\text{C}_{10'}$), 134.2 (d, $^3J(\text{C-P}) = 5.2$, $\text{C}_{9'}$), 139.2 (s, $\text{C}_{8'}$).

m/z (EI) 334 (M^+ , 2 %), 161 (29), 147 (100).

4.7.4. Diethyl 1,1-difluoro 2-hydroxy 2-methyl 2-(2'-thienyl) ethylphosphonate **8d**

^{31}P NMR (CDCl_3): δ +5.2 (t, $^2J(\text{P-F}) = 103$) ; ^1H NMR (CDCl_3): δ 1.14 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 1.37 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 1.73 (t, 3H, CH_3), 3.7-4.2 (m, 2H, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 4.29 (p, 2H, $^3J(\text{H-P}) = ^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 7.00 (dd, 1H, $^3J(\text{H-H}) = 5.0$, $^3J(\text{H-H}) = 3.7$, H_4 of $\text{C}_4\text{H}_3\text{S}$), 7.10 (d, 1H, $^3J(\text{H-H}) = 3.7$, H_3 of $\text{C}_4\text{H}_3\text{S}$), 7.29 (d, 1H, $^3J(\text{H-H}) = 5.0$, $^4J(\text{H-H}) = 1.2$, H_5 of $\text{C}_4\text{H}_3\text{S}$) ; ^{13}C NMR (CDCl_3): δ 16.2 (d, $^3J(\text{C-P}) = 6.3$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 16.2 (d, $^3J(\text{C-P}) = 5.8$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 24.6 (t, $^3J(\text{C-P}) = 2.2$, CH_3), 64.9 (d, $^2J(\text{C-P}) = 6.5$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 64.9 (d, $^2J(\text{C-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 75.6 (td, $^2J(\text{C-F}) = 23.2$, $^2J(\text{C-P}) = 15.0$, PCF_2COH), 118.8 (td, $^1J(\text{C-F}) = 273.0$, $^1J(\text{C-P}) = 202.9$, PCF_2COH), 125.5 (s, C_3 of $\text{C}_4\text{H}_3\text{S}$), 125.6 (s, C_4 of $\text{C}_4\text{H}_3\text{S}$), 126.8 (s, C_5 of $\text{C}_4\text{H}_3\text{S}$), 145.2 (s, C_2 of $\text{C}_4\text{H}_3\text{S}$).

m/z (EI) 314 (M^+ , 22 %), 188 (66), 161 (95), 127 (100).

4.8. General procedure for the transposition of the diethyl 1,1-difluoro 2-hydroxyethyl phosphonates **7** and **8** into **9** and **10**.

Sodium hydride (0.15 g of 60% dispersion in mineral oil, 3.3 mmol) was washed with hexane (3 x 10 ml) in a three-necked round bottom flask equipped with a thermometer, reflux condenser and an addition funnel and flushed with nitrogen. Magnetic stirring was initiated and THF (20 ml) was added. The suspension was cooled to 0°C , diethyl 1,1-difluoro-2-hydroxyethyl phosphonate (**7** or **8**, 3 mmol) was then added dropwise. After an additional 30 min at 0°C , a ice-cold mixture of water (10 ml) and brine (10ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were dried (MgSO_4) and the solvents were removed under reduced pressure to give the crude product (**9** or **10**) which was purified by chromatography.

4.8.1. Diethyl 1-heptyl 2,2-difluoroethylphosphate **9a**

^{31}P NMR (CDCl_3): δ -3.4 (s) ; ^1H NMR (CDCl_3): δ 0.85 (t, 3H, $^3J(\text{H-H}) = 6.4$, $(\text{CH}_2)_6\text{CH}_3$), 1.28 (m, 14H, $(\text{CH}_2)_4\text{CH}_3$ and $\text{CH}_3\text{CH}_2\text{O}$), 1.47 (m, 2H, $\text{CH}(\text{OP})\text{CH}_2\text{CH}_2$), 1.68 (m, 2H, $\text{CH}(\text{OP})\text{CH}_2$), 4.12 (qd, 4H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.2$, $\text{CH}_3\text{CH}_2\text{O}$), 4.45 (m, 1H, $\text{HF}_2\text{C-CH}$), 5.80 (td, 1H, $^2J(\text{H-F}) = 55.3$, $^3J(\text{H-H}) = 3.4$, HF_2C) ; ^{13}C NMR (CDCl_3): δ 14.6 (s, $(\text{CH}_2)_6\text{CH}_3$), 16.5 (d, $^3J(\text{C-P}) = 2.7$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 16.6 (d, $^3J(\text{C-P}) = 3.0$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 23.2 (s, CH_2), 24.9 (s, CH_2), 29.1 (s, CH_2), 29.8 (s, CH_2), 30.0 (s, CH_2), 32.4 (s, CH_2), 64.7 (d, $^2J(\text{C-P}) = 6.1$, $\text{CH}_3\text{CH}_2\text{O}$), 76.7 (td, $^2J(\text{C-F}) = 25.1$, $^2J(\text{C-P}) = 5.8$, $\text{HF}_2\text{C-CH}$), 114.7 (td, $^1J(\text{C-F}) = 245.0$, $^3J(\text{C-P}) = 4.9$, HF_2C).

m/z (CI +ve) 317 ($\text{M}+\text{H}^+$, 100 %).

4.8.2. Diethyl 1-(1'-methyl)propyl 2,2-difluoroethylphosphate (two diastereomers) **9b**

^{31}P NMR (CDCl_3): δ -3.2 (s, maj.), -3.3 (s, min.) ; ^1H NMR (CDCl_3): δ 0.92 (t, 3H, $^3J(\text{H-H}) = 7.3$, $\text{CH}_2\text{-CH}_3$ min.), 0.94 (t, 3H, $^3J(\text{H-H}) = 7.3$, $\text{CH}_2\text{-CH}_3$ maj.), 0.98 (d, 3H, $^3J(\text{H-H}) = 6.9$, CH-CH_3 maj.), 1.02 (d, 3H, $^3J(\text{H-H}) = 7.0$, CH-CH_3 min.), 1.3 (m_{masked}, 1H, CHH-CH_3), 1.32 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.54 (m, 1H, CHH-CH_3), 1.83 (m, 1H, CH-CH_3), 4.12 (p, 4H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.2$, $\text{CH}_3\text{CH}_2\text{O}$), 4.4 (m, 1H, $\text{HF}_2\text{C-CH}$), 5.81 (td, 1H, $^2J(\text{H-F}) = 55.2$, $^3J(\text{H-H}) = 4.7$, $\text{HF}_2\text{C}_{\text{maj.}}$), 5.85 (td, 1H, $^2J(\text{H-F}) = 54.8$, $^3J(\text{H-H}) = 3.9$, $\text{HF}_2\text{C}_{\text{min.}}$) ; ^{13}C NMR (CDCl_3): δ 11.1 (s, CH_2CH_3 min.), 11.5 (s, CH_2CH_3 maj.), 13.4 (s, CHCH_3 maj.), 14.4 (s, CHCH_3 min.), 15.9 (d, $^3J(\text{C-P}) = 3.4$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 16.0 (d, $^3J(\text{C-P}) = 4.4$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 24.0 (s, CH_2CH_3 min.), 25.8 (s, CH_2CH_3 maj.), 35.2 (q, $^3J(\text{C-F}) = ^3J(\text{C-P}) = 3.0$, CHCH_3 maj.), 35.6 (q, $^3J(\text{C-F}) = ^3J(\text{C-P}) = 3.0$, CHCH_3 min.), 64.0 (d, $^2J(\text{C-P}) = 5.9$, $\text{CH}_3\text{CH}_2\text{O}$), 78.5 (td, $^2J(\text{C-F}) = 24.1$, $^2J(\text{C-P}) = 5.9$, $\text{HF}_2\text{C-CH}_{\text{maj.}}$), 79.5 (td, $^2J(\text{C-F}) = 23.4$, $^2J(\text{C-P}) = 5.9$, $\text{HF}_2\text{C-CH}_{\text{min.}}$), 114.2 (td, $^1J(\text{C-F}) = 244.4$, $^3J(\text{C-P}) = 4.8$, $\text{HF}_2\text{C}_{\text{min.}}$), 114.4 (td, $^1J(\text{C-F}) = 244.5$, $^3J(\text{C-P}) = 4.5$, $\text{HF}_2\text{C}_{\text{maj.}}$).

m/z (CI +ve) 275 ($\text{M}+\text{H}^+$, 100 %).

4.8.3. Diethyl 1-(1',1'-dimethyl)ethyl 2,2-difluoroethylphosphate **9c**

^{31}P NMR (CDCl_3): δ -3.2 (s) ; ^{19}F NMR (CDCl_3): δ -123.7 (ddd, A part of ABXY system, $^2J(\text{F-F}) = 289.4$, $^2J(\text{F-H}) = 53.3$, $^3J(\text{F-H}) = 11.4$, $\text{H}_\text{X}\text{E}_\text{A}\text{F}_\text{B}\text{CCH}_\text{Y}$), -125.6 (ddd, B part of ABXY system, $^2J(\text{F-F}) = 289.4$, $^2J(\text{F-H}) = 53.3$, $^3J(\text{F-H}) = 11.4$, $\text{H}_\text{X}\text{F}_\text{A}\text{E}_\text{B}\text{CCH}_\text{Y}$) ; ^1H NMR (CDCl_3): δ 1.04 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.33 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.14 (p, 4H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.23 (dddd, 1H, $^3J(\text{H-P}) = 15.9$, $^3J(\text{H-F}) = 10.3$, $^3J(\text{H-F}) = 9.6$, $^3J(\text{H-H}) = 2.8$, $\text{HF}_2\text{C-CH}$), 5.88 (td, 1H, $^2J(\text{H-F}) = 54.0$, $^3J(\text{H-H}) = 2.8$, HF_2C) ; ^{13}C NMR (CDCl_3): δ 15.7 (d, $^3J(\text{C-P}) = 5.0$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 15.8 (d, $^3J(\text{C-P}) = 5.0$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 25.8 (s, $\text{C}(\text{CH}_3)_3$), 33.6 (t, $^3J(\text{C-F}) = 3.4$, $\text{C}(\text{CH}_3)_3$), 63.7 (d, $^2J(\text{C-P}) = 6.0$, $\text{CH}_3\text{CH}_2\text{O}$), 82.4 (ddd, $^2J(\text{C-F}) = 21.4$, $^2J(\text{C-F}) = 18.7$, $^2J(\text{C-P}) = 6.1$, $\text{HF}_2\text{C-CH}$), 113.8 (ddd, $^1J(\text{C-F}) = 246.3$, $^1J(\text{C-F}) = 243.5$, $^3J(\text{C-P}) = 2.7$, HF_2C).

m/z (CI +ve) 275 ($\text{M}+\text{H}^+$, 100 %).

4.8.4. Diethyl 1-(4'-fluoro)phenyl 2,2-difluoroethylphosphate **9e**

^{31}P NMR (CDCl_3): δ -3.6 (s) ; ^{19}F NMR (CDCl_3): δ -112.6 (s, $\text{C}_6\text{H}_5\text{F}$), -127.5 (ddd, A part of ABXY system, $^2J(\text{F-F}) = 285.6$, $^2J(\text{F-H}) = 53.3$, $^3J(\text{F-H}) = 11.4$, $\text{H}_\text{X}\text{E}_\text{A}\text{F}_\text{B}\text{CCH}_\text{Y}$), -130.3 (ddd, B part of ABXY system, $^2J(\text{F-F}) = 285.6$, $^2J(\text{F-H}) = 53.3$, $^3J(\text{F-H}) = 11.4$, $\text{H}_\text{X}\text{F}_\text{A}\text{E}_\text{B}\text{CCH}_\text{Y}$) ; ^1H NMR (CDCl_3): δ 1.17 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 1.28 (t, 3H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 3.94 (pd, 2H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.1$, $J = 2.5$, $\text{CH}_3\text{CH}_2\text{O}_\text{A}$), 4.09 (q, 2H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_\text{B}$), 5.36 (qd, 1H, $^3J(\text{H-P}) = ^3J(\text{H-F}) = 10.1$, $^3J(\text{H-H}) = 4.0$, $\text{HF}_2\text{C-CH}$), 5.88 (td, 1H, $^2J(\text{H-F}) = 55.2$, $^3J(\text{H-H}) = 4.0$, HF_2C), 7.09 (t, 2H, $^3J(\text{H-H}) = ^3J(\text{H-F}) = 8.7$, H_{meta} of $\text{C}_6\text{H}_4\text{F}$), 7.41 (dd, 2H, $^3J(\text{H-H}) = ^3J(\text{H-F}) = 8.7$, $^3J(\text{H-F}) = 5.3$, H_{ortho}

of C₆H₄F) ; ¹³C NMR (CDCl₃): δ 16.2 (d, ³J(C-P) = 3.0, CH₃CH₂O_A), 16.3 (d, ³J(C-P) = 3.8, CH₃CH₂O_B), 64.6 (d, ²J(C-P) = 6.0, CH₃CH₂O_A), 64.8 (d, ²J(C-P) = 6.2, CH₃CH₂O_B), 77.1 (td, ²J(C-F) = 26.6, ²J(C-P) = 4.7, HF₂C-CH), 114.1 (td, ¹J(C-F) = 246.6, ³J(C-P) = 8.7, HF₂C), 116.2 (d, ³J(C-F) = 22.2, C_{meta} of C₆H₄F), 129.2 (s_{large}, C_{ipso} of C₆H₄F), 130.2 (d, ⁴J(C-F) = 8.2, C_{ortho} of C₆H₄F), 163.8 (d, ¹J(C-F) = 248.7, C_{para} of C₆H₄F).

m/z (EI) 313 (M+H⁺, 1 %), 292 (44), 244 (55), 216 (84).

4.8.5. Diethyl 1-(4'-methyl)phenyl 2,2-difluoroethylphosphate **9f**

³¹P NMR (CDCl₃): δ -3.8 (s) ; ¹H NMR (CDCl₃): δ 1.16 (t, 3H, ³J(H-H) = 7.1, CH₃CH₂O_A), 1.27 (t, 3H, ³J(H-H) = 7.1, CH₃CH₂O_B), 2.35 (s, 3H, C₆H₄CH₃), 3.92 (pd, 2H, ³J(H-H) = ³J(H-P) = 7.1, J = 3.2, CH₃CH₂O_A), 4.10 (q, 2H, ³J(H-H) = 7.1, CH₃CH₂O_B), 5.33 (qd, 1H, ³J(H-P) = ³J(H-F) = 10.0, ³J(H-H) = 4.2, HF₂C-CH), 5.87 (td, 1H, ²J(H-F) = 55.3, ³J(H-H) = 4.2, HF₂C), 7.20 (d, 2H, ³J(H-H) = 7.9, H_{meta} of C₆H₄CH₃), 7.30 (d, 2H, ³J(H-H) = 7.9, H_{ortho} of C₆H₄CH₃) ; ¹³C NMR (CDCl₃): δ 15.7 (d, ³J(C-P) = 4.8, CH₃CH₂O_A), 15.8 (d, ³J(C-P) = 3.6, CH₃CH₂O_B), 21.1 (s, C₆H₄CH₃), 64.1 (d, ²J(C-P) = 6.1, CH₃CH₂O_A), 64.2 (d, ²J(C-P) = 6.1, CH₃CH₂O_B), 77.5 (td, ²J(C-F) = 26.2, ²J(C-P) = 5.0, HF₂C-CH), 114.1 (td, ¹J(C-F) = 245.8, ³J(C-P) = 9.0, HF₂C), 127.7 (s, C_{ortho} of C₆H₄CH₃), 129.4 (s, C_{meta} of C₆H₄CH₃), 130.1 (s_{large}, C_{ipso} of C₆H₄CH₃), 139.6 (s, C_{para} of C₆H₄CH₃).

m/z (EI) 309 (M+H⁺, 1 %), 288 (100).

4.8.6. Diethyl 1-(4'-methoxyphenyl) 2,2-difluoroethylphosphate **9g**

³¹P NMR (CDCl₃): δ -3.7 (s) ; ¹H NMR (CDCl₃): δ 1.13 (t, 3H, ³J(H-H) = 7.1, CH₃CH₂O_A), 1.24 (t, 3H, ³J(H-H) = 7.1, CH₃CH₂O_B), 3.77 (s, 3H, C₆H₄OCH₃), 3.88 (pd, 2H, ³J(H-H) = ³J(H-P) = 7.1, J = 3.2, CH₃CH₂O_A), 4.07 (m, 2H, CH₃CH₂O_B), 5.30 (qd, 1H, ³J(H-P) = ³J(H-F) = 10.0, ³J(H-H) = 4.1, HF₂C-CH), 5.85 (td, 1H, ²J(H-F) = 55.3, ³J(H-H) = 4.1, HF₂C), 6.88 (d, 2H, ³J(H-H) = 8.7, H_{meta} of C₆H₄OCH₃), 7.32 (d, 2H, ³J(H-H) = 8.7, H_{ortho} of C₆H₄OCH₃) ; ¹³C NMR (CDCl₃): δ 15.7 (d, ³J(C-P) = 4.2, CH₃CH₂O_A), 15.8 (d, ³J(C-P) = 4.5, CH₃CH₂O_B), 55.1 (s, C₆H₄OCH₃), 64.0 (d, ²J(C-P) = 6.9, CH₃CH₂O_A), 64.1 (d, ²J(C-P) = 7.0, CH₃CH₂O_B), 77.2 (td, ²J(C-F) = 26.2, ²J(C-P) = 5.0, HF₂C-CH), 114.1 (s, C_{meta} of C₆H₄OCH₃), 114.1 (td, ¹J(C-F) = 245.9, ³J(C-P) = 9.2, HF₂C), 125.0 (d, ³J(C-P) = 2.0, C_{ipso} of C₆H₄OCH₃), 129.3 (s, C_{ortho} of C₆H₄OCH₃), 160.7 (s, C_{para} of C₆H₄OCH₃).

m/z (EI) 324 (M⁺, 3 %), 304 (100).

4.8.7. Diethyl 1-(2'-pyridyl) 2,2-difluoroethylphosphate **9k**

^{31}P NMR (CDCl_3): δ -4.0 (s) ; ^1H NMR (CDCl_3): δ 1.31 (q, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_A$ and B), 4.1 (m, 2H, $\text{CH}_3\text{CH}_2\text{O}_A$), 4.21 (p, 2H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}_B$), 5.52 (qd, 1H, $^3J(\text{H-P}) = ^3J(\text{H-F}) = 10.3$, $^3J(\text{H-H}) = 3.6$, $\text{HF}_2\text{C-CH}$), 6.22 (td, 1H, $^2J(\text{H-F}) = 54.7$, $^3J(\text{H-H}) = 3.6$, HF_2C), 7.30 (dd, 1H, $^3J(\text{H-H}) = 7.7$ and 4.8, $\text{H}_{5'}$ of $\text{C}_5\text{H}_4\text{N}$), 7.53 (d_{large} , 1H, $^3J(\text{H-H}) = 7.7$, $\text{H}_{3'}$ of $\text{C}_5\text{H}_4\text{N}$), 7.76 (td, 1H, $^3J(\text{H-H}) = 7.7$, $^4J(\text{H-H}) = 1.8$, $\text{H}_{4'}$ of $\text{C}_5\text{H}_4\text{N}$), 8.61 (dd, 1H, $^3J(\text{H-H}) = 4.8$, $^4J(\text{H-H}) = 1.8$, $\text{H}_{6'}$ of $\text{C}_5\text{H}_4\text{N}$) ; ^{13}C NMR (CDCl_3): δ 15.8 (t, $^3J(\text{C-P}) = 7.0$ and 6.0, $\text{CH}_3\text{CH}_2\text{O}_A$ and B), 64.3 (t, $^2J(\text{C-P}) = 6.8$ and 7.1, $\text{CH}_3\text{CH}_2\text{O}_A$ and B), 77.4 (ddd, $^2J(\text{C-F}) = 27.1$ and 22.7, $^2J(\text{C-P}) = 4.6$, $\text{HF}_2\text{C-CH}$), 119.0 (td, $^1J(\text{C-F}) = 248.2$, $^3J(\text{C-P}) = 5.6$, HF_2C), 122.7 (s, $\text{C}_{3'}$ of $\text{C}_5\text{H}_4\text{N}$), 124.2 (s, $\text{C}_{5'}$ of $\text{C}_5\text{H}_4\text{N}$), 137.2 (s, $\text{C}_{4'}$ of $\text{C}_5\text{H}_4\text{N}$), 149.4 (s, $\text{C}_{6'}$ of $\text{C}_5\text{H}_4\text{N}$), 153.0 (d, $^3J(\text{C-P}) = 2.8$, $\text{C}_{2'}$ of $\text{C}_5\text{H}_4\text{N}$).

m/z (EI) 295 (M^+ , 31 %), 275 (45), 250 (52), 227 (82).

4.8.8. Diethyl (1'-difluoromethyl)cyclohexylphosphate **10a**

^{31}P NMR (CDCl_3): δ -7.5 (s) ; ^{19}F NMR (CDCl_3): δ -133.9 (d, $^2J(\text{F-H}) = 57.1$, HF_2CCOP) ; ^1H NMR (CDCl_3): δ 1.18 (m, 1H, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 1.32 (t, 6H, $^3J(\text{H-H}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.62 (m + d, 7H, $^3J(\text{H-H}) = 6.3$, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 2.09 (d_{large} , 2H, $^3J(\text{H-H}) = 10.5$, $\text{COH}(\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2)_2\text{CH}_2$), 4.10 (p, 4H, $^3J(\text{H-H}) = ^3J(\text{H-P}) = 7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 6.12 (t, 1H, $^2J(\text{H-F}) = 56.2$, HF_2C) ; ^{13}C NMR (CDCl_3): δ 16.3 (d, $^3J(\text{C-P}) = 7.5$, $\text{CH}_3\text{CH}_2\text{O}$), 20.8 (s, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 25.3 (s, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 29.1 (t, $^3J(\text{C-F}) = 3.1$, $\text{COH}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 64.2 (d, $^2J(\text{C-P}) = 6.2$, $\text{CH}_3\text{CH}_2\text{O}$), 83.5 (td, $^2J(\text{C-F}) = 22.7$, $^2J(\text{C-P}) = 7.5$, $\text{HF}_2\text{C-CH}$), 115.3 (t, $^1J(\text{C-F}) = 247.3$, HF_2C).

m/z (CI +ve) 287 ($\text{M}+\text{H}^+$, 100 %).

4.8.9. 1,1-Difluoro 2-(4'-dimethylamino)phenyl ethene issued from **7h**

^1H NMR (CDCl_3): δ 2.98 (s, 6H, $\text{N}(\text{CH}_3)_2$), 5.20 (dd, 1H, $^3J(\text{H-Ftrans}) = 26.9$, $^3J(\text{H-Fcis}) = 4.0$, $\text{F}_2\text{C=CH}$), 6.72 (d, 2H, $^3J(\text{H-H}) = 8.8$, H_{meta} of C_6H_4), 7.24 (d, 2H, $^3J(\text{H-H}) = 8.8$, H_{ortho} of C_6H_4).

m/z (EI) 183 (M^+ , 100 %), 167 (44).

4.8.10. (1-Difluoromethylene-1,2,3,4-tetrahydro)naphthyl issued from **8c**

^1H NMR (CDCl_3): δ 1.92 (pd, 2H, $^3J(\text{H-H}) = 6.3$, $^5J(\text{H-F}) = 1.6$, H_3), 2.55 (m, 2H, H_2), 2.87 (t, 2H, $^3J(\text{H-H}) = 6.3$, H_4), 7.15 (m, 3H, H_5 , 6 and 7), 7.65 (d_{large} , 1H $^5J(\text{H-F}) = 6.3$, H_8) ; ^{13}C NMR (CDCl_3): δ 24.0 (s, C_3), 30.5 (s, C_4), 31.1 (s, C_2), 89.0 (dd, $^2J(\text{C-F}) = 22.4$ and 10.0, C_1), 126.9 (s, C_6), 127.3 (s, C_7), 127.9 (d, $^4J(\text{C-F}) = 13.9$, C_8), 129.7 (s, C_5 and C_{10}), 138.2 (d, $^3J(\text{C-F}) = 4.0$, C_9), 153.6 (dd, $^1J(\text{C-F}) = 294.7$ and 285.2, $=\text{CF}_2$).

m/z (EI) 180 (M^+ , 35), 147 (70), 129 (100).

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